13

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/684,151	**Applicant(s)** SEGALL ET AL.
	Examiner Brian S. Kwon	**Art Unit** 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) *21-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *06/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, with traverse, with the Group II, claims 31-40, is acknowledged. Applicants traverse the restriction requirement on the grounds that there would be no burden in searching the entire groups. This argument is not persuasive, as claimed invention would be distinctive, each from the other for the reason of the record. Furthermore, the search of the entire groups in the non-patent literature (a significant part of a through examination) would be burdensome. Therefore. The requirement is still deemed proper, and made Final. Claims 21-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 31-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific dynamic buffering system such as carboxylic acid, salt or ester and the specific oncotic agent such as hydroxyethyl starch and dextran, does not reasonably provide enablement for "a dynamic buffering system" and "oncotic agent" or "oncotinc agent having different clearing rates". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claims are directed to a process of administering a composition comprising electrolytes, a dynamic buffering system and at least a first oncotic agent and a second oncotic agent having differential clearing rates, wherein said solution does not comprise a biological buffer, to a patient (intended purpose of replacing blood in the patient).

The instant specification discloses that the term "dynamic buffering system" refers to "one or more reagents that work in combination to keep the pH of the solution in a certain range in an in vivo environment" and "oncotic agent" (page 5, lines 18-20); and the term "oncotic agent" is included of molecules whose size is sufficient to prevent its loss from the circulation by readily traversing the fenestrations of the capillary bed into the interstitial spaces of the tissues of the body" (page 7, lines 9-12).

The state of the art recognizes the term "buffer" as a solution containing either a weak acid and its salt or a weak base and its salt, which is resistant to changes in pH (see thefreedictionary.com). For example, acetic acid, phosphoric acid, oxalic acid, carbonic acid, sodium acetate, potassium phosphate, lithium oxalate, ammonium hydroxide, sodium hydroxide, ammonium acetate, 4-ethylmorpholine, sodium hydrogen carbonate, sodium lauryl sulfate and 2, 4,6-Tris(dimethylaminomethyl)phenol are used as buffering substance. Especially in blood plasma art, biological buffers such as HEPES, TRIS, BIS-TRIS lactate and a balanced solution of Trizma base and Trizma HCl in lieu of lactate or bicarbonate, sodium acetate are routinely utilized in preparing blood substitute.

The term "oncotic" means "of or caused by a condition of swelling" (see thefreedicitionary.com). In the blood plasma art, "oncotic agent" refers to an agent to maintain physiological osmotic pressure in the blood plasma (see "oncotic pressure", www.aswers.com).

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instantly claimed "a dynamic buffering system" and "oncotic agent". Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the instantly claimed "a dynamic buffering system" and "oncotic agent" is very broad due to their generic definition. The instant claims read on any compound having characteristic of "one or more reagents that work in combination to keep the pH of the solution in a certain range in an in vivo environment" or "an agent to maintain physiological osmotic pressure in the blood plasma, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Furthermore, the instant claims cover "a dynamic buffering system" and "oncotic agent" that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

As discussed above, in the instant case, only a limited number of "a dynamic buffering system" and "oncotic agent" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of diseases required. Applicant fails to provide information allowing the skilled artisan to ascertain suitable "a dynamic buffering system" and "oncotic agent" without undue experimentation.

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of "a dynamic buffering system" and "oncotic agent" that would enabled in this specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 31-40 are rejected under 35 USC 103(a) as being unpatentable over either Segall et al. (WO 92/18136) in view of Altura et al. ("Ca2+ coupling in vascular smooth muscle: Mg2+ and buffer effects on contractility and membrane Ca2+ movements", Canadian Journal of Physiology and Pharmacology, 1982, 60(4) 459-82), and further in view of Segall (US 5945272).

The amended claims now read on a method of administering a composition comprising a physiologically acceptable aqueous solution comprising electrolytes, a dynamic buffering system comprising a carboxylic acid, salt or ester thereof, at least one oncotic agent having differential clearance rate, further wherein said solution does not comprise a biological buffer, to a patient in a hyperbaric oxygen chamber. Further limitations include "said first and second oncotic agents have different molecular weidht" (claim 32); "said first oncotic agent is a low to medium molecular weight onctoic agent and said second oncotic agent is a high molecular weight oncotic agent" (claim 33); "said first and second oncotic agent are polysaccharides" (claim 34); "hydroxethyl starches" (claim 35); "clearance rates differ by about 2 fold" (claim 36); "said first oncotic agent has a clearance rate of 2 to 3 hours and said second oncotic agent has a clearance rate of 6 hours" (claim 37); "carboxylic acid, salt, or ester thereof is selected from the group consisting of lactate, acetate, gluconate, citrate and pyruvate" (claim 39); and "said dynamic buffering system further comprises bicarbonate" (claim 40).

Segall (WO 92/18136) teaches a blood substitute composition comprising electrolytes (e.g., sodium and calcium), magnesium, glucose, carboxylic acid salt (e.g., sodium gluconate), two or more oncotic agents (e.g., high molecular hydroxyethyl starch, low molecular hydrxyethyl starch, dextran 40 and dextran 70) and biological buffer (e.g., TRIS, HEPES, TES, MOPS, TAPSO, EPPS). See page 8, line 15 thru page 20, line 32 and Examples. The reference also teaches (i) the use of mixtures of carboxylic acid salt (e.g., sodium citrate, sodium gluconate, sodium pyruvate, sodium succinate, sodium bicarbonate and sodium lactate) in said composition (page 7, line 31 thru page 10, line 11); (ii) the use of simple hexose sugar (e.g., glucose, fructose and galactose) in the range of upto about 50nM, preferably in the range between 2 mM and 10mM (page 10, lines 9-24); (iii) the method of perfusing a subject prepared for circulatory perfusion (claim 41 and 45) whereby positioning said patient in a hyperbaric oxygen chamber (page 16, lines 23-31; Examples 4 and 7).

Altura teaches or suggests the disadvantage of using conventional buffers (e.g., TRIS, HEPES, MOPS, PIPES and bicine) in physiological solution because they can exert adverse effects on contractility and reactivity of certain arterial and venous smooth muscles.

Segall'272 teaches the use of one or more of oncotic agents having differential clearance rates, for example high molecular weight hetastarch (molecular weight 300,000-1,000,000) and dextran 70, measured to have intravascular persistence rates of 6 hrs or low molecular weight hetastarch (average molecular weight 40,0000-200,000) and dextran 40, having intravascular persistence rates of 2-3 hours, in the blood substitute composition (column 7, lines 37-64).

The claimed invention differs from the references (Segall WO 92/18136 or US 5130230) in the exclusion of conventional buffer and plurality of oncotic agents having differential clearance rates. To incorporate such teaching into the teaching of Segall (WO 92/18136), would have been obvious in view of Altura who teaches or suggests the disadvantage of using the conventional buffers in physiological solution and Segall'272 who teaches the advantage of using one or more of oncotic agents (i.e., high molecular hetarstarch and dextran 70 or low molecular hetastarch and dextran 40) in restoring blood onctoic pressure in a hypovolemic subject over an extended period of time.

One having ordinary skill in the art would have been motivated to modify the teaching of Segall (WO 92/18136) such that the adverse effects associated with the use of conventional buffer such as TRIS, HEPES, MOPS and PIPES in said composition would be greatly eliminated. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 31-40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. US 6680305, claims 1-12 of U.S. Patent No. 6284452, claims 13-15 of U. S. Patent No. 5407428, claims 21 of U.S. No. 6300322 and claims 1-11 or U.S. No. 6991624 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly required "positioning said subject in a hyperbaric oxygen chamber" and plurality of oncotic agents having differential clearing rates would have been obvious to a person of the ordinary skill in the art as reasoned below.

Both of the instant application and the patent are directed to the using of same active and inactive ingredients in a composition, wherein said composition is administered to patients (in hyperbaric oxygen chamber, see for example claim 11 of US'624; column 10, lines 32-53 of US'322; column 7, line 66 thru column 8, line 11 of US'452; column 10, line 51 thru column 12, line 20 of US'305) intended for the same ultimate purpose. The claimed high molecular weight hetastarch (molecular weight 300,000-1,000,0000) and dextran 70 having intravscualr persistence rates of 6 hours or low molecular weight hetastarch (molecular weight 40,000-200,0000) and dextran having intravascular persistence rates of 2-3 hours are disclosed in the prior art references. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. One having ordinary skill in the art at the time of the invention was made would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

5. In looking in continuity data, it is noted that applicant has numerous issued patent and pending applications encompassing the same or similar subject matter of the instant application. Applicant should review all subject matter considered the same or similar, and submit the

appropriate Terminal Disclaimer(s). For example, U.S Application No. 10/641401 and US Patent No. 5702880 to be same or similar subject matter(s).

Conclusion

6. No Claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614